Analysis of Zone and Pump Configurations in Simulated Moving Bed Purification of Insulin

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The effects of pump failures in nine zone and pump configurations for the size-exclusion simulated moving bed purification of insulin are analyzed. Simulations based on verified intrinsic parameters are used to understand the dynamic wave phenomena. This understanding helps determine the best zone and pump configuration, determine the time window to recover from the degraded state, and formulate contingency responses to failures. The results show that the open-loop three-zone simulated moving bed is the best. It is more reliable, and has higher productivity and reduced residence time of the high molecular weight impurities. A disadvantage of the three-zone is the higher solvent consumption. In the recommended configuration: desorbent pump failure is critical and dual redundant pumps are recommended; feed pump failure is marginal and results in diluted product; and zone II pump failure is critical—the time window for corrective action is half a step-time. Zone pumps are recommended instead of outlet pumps because they do not result in stationary phase collapse from high pressure drop and allow higher productivity in pressure-limited systems. © 2006 American Institute of Chemical Engineers *AIChE J,* 52: 2447–2460, 2006
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Introduction

Simulated Moving Bed (SMB) chromatography can achieve both high product yield and purity while improving productivity, solvent, manpower, and floorspace utilizations over conventional batch chromatography. A standard four-zone SMB, as illustrated in Figure 1a, is inherently a binary separation method. A multi-component mixture can be separated into three separate streams with two SMB rings in series (tandem SMB).[1] Each ring removes either the fast or slow moving impurities completely. Other SMB schemes for multi-component separation exist.[2,3]

We have designed and verified experimentally a tandem SMB for insulin purification.[1,4,5] The size-exclusion SMB is designed to remove two impurities, zinc chloride and high molecular weight proteins or HMWP, before final crystallization. The elution order is HMWP, insulin, and zinc chloride. This work has been extended to include robust design,[6] system optimization,[7] residence time study of the solute,[8,9] maintenance of batch identity,[10] fast startup and shutdown process-

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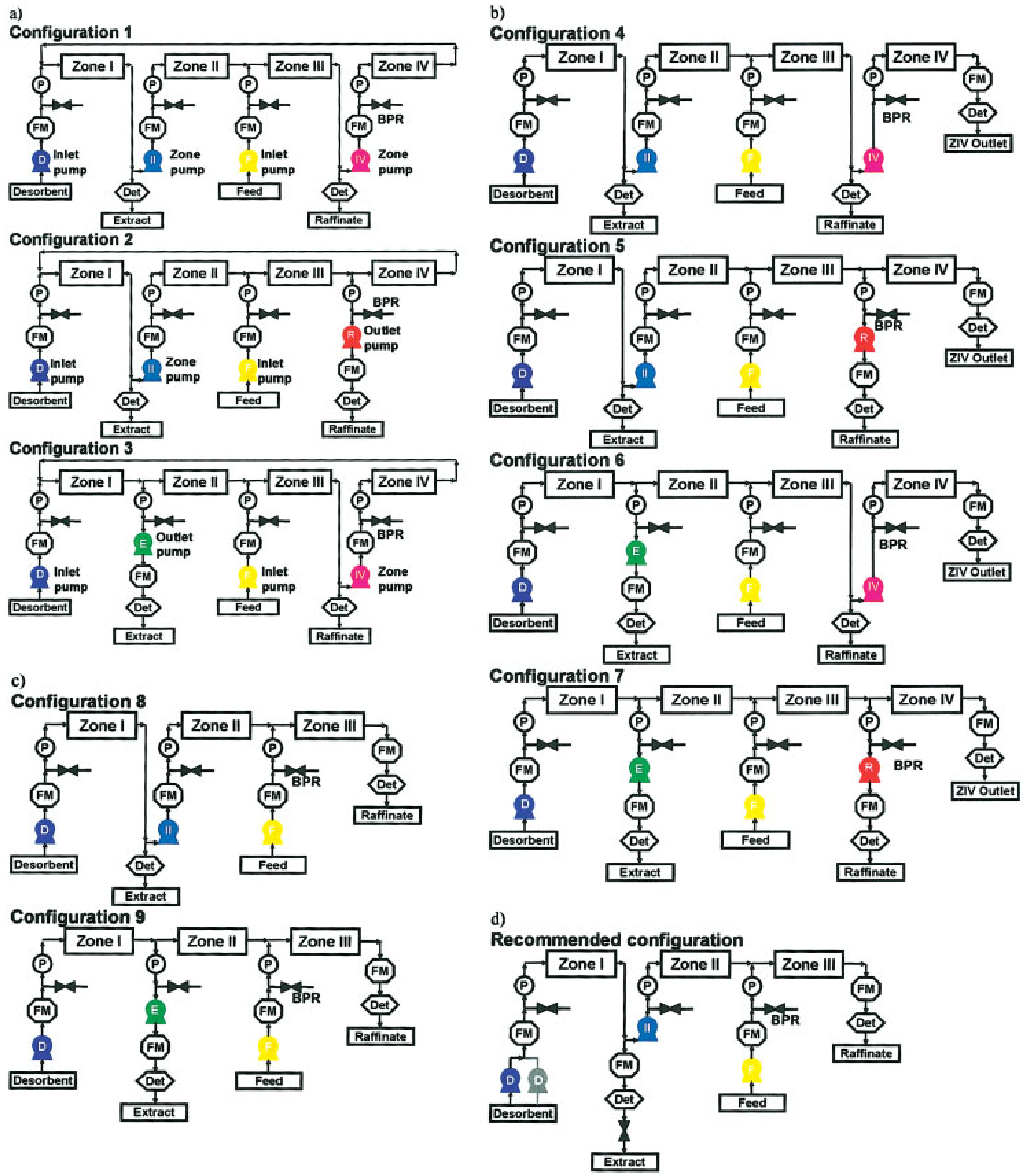

Figure 1. Zone and pump configurations.

(a) Four-zone closed-loop SMB, (b) Four-zone open-loop SMB, (c) Three-zone open-loop SMB, and d) Recommended configuration. (BPR stands for Back Pressure Regulators, DET for detector, FM for flowmeter, and P for pressure gage.) [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

es,[11] periodic regeneration in SMB,[12] and the use of Chelex 100 columns to remove zinc chloride.[13]

SMB, while a more efficient system, has larger product lots within the process and thus a higher cost in the event of a failure. Furthermore, an SMB operation is much more complex and thus has a higher likelihood of failure than a comparable batch operation. The periodic port movement and cyclic nature of SMB operation result in more complex responses, and thus, produce potential failures that are more difficult to diagnose. These factors and other SMB advances (such as non-synchronous switching[14]) contribute to the challenges of identifying the potential failures and their effects on the product purity and yield, and of determining the diagnostic and contingency responses to these potential failures.

This study applies failure analysis to improve the robustness, reliability, and safety of SMB for size exclusion purification of insulin. Failure analysis is, in short, an iterative design and risk management tool. The three critical SMB components for investigation are the pumps, valves, and columns with the stationary phase. In this study, we focus on the pump failure mode of no flow through a pump for different pump configurations. The result of this particular study in turn simplifies subsequent analyses of valve and column failures (such as drifts).

The intent of this study is to minimize the product yield loss by careful selection of zone and pump configurations, and placement of flowmeters and pressure sensors. This is achieved through systematic analyses of the pressure drop and the dynamic wave phenomena in the event of a pump failure. Rate model simulations help elucidate the dynamics and the impact of the failure. We will then recommend design changes and contingency actions to minimize the occurrence and the effects of the failure events.

We will attempt to answer the following questions: What failures affect yield, purity, or system performance? What failures lead to safety concerns? How are the effects detected? How soon can the failures be detected? What are the responses upon failure detection? What is the time window to allow the system to recover completely from the degraded state?

This is the first attempt at applying failure analysis to investigate zone configuration and pump placement in SMB. To our best knowledge, there is no published SMB literature that directly addresses the aforementioned questions. However, sensitivity analyses of column homogeneity or operating parameters of the system have been reported.[6,15-20]

The general approach in this study involves identifying the common SMB zone configurations and their corresponding pump configurations. We then select a benchmark from the insulin purification literature as a representative example. Both the immediate and delayed failure effects of each pump failure case are studied. The immediate effects are changes in the system pressure drops as a result of changing flowrate. The delayed effects are dynamic changes in the concentration profiles and histories. Rate-model simulations using verified parameters are used to examine the dynamic wave phenomena for each failure case. From the failure effects, the most robust configuration is identified. Finally, for the recommended configuration, simulations are used to find the time window for taking corrective actions to minimize yield loss and product contamination.

The recommended pump configuration for size exclusion insulin purification is a three-zone open-loop SMB with dual desorbent and zone II pumps (Figure 1d). Three-zone SMBs are more reliable, have higher productivity, have shorter residence time for raffinate solutes,[9] and prevent wrap-around of the low affinity solutes. The desorbent pump is the most important pump and the system reliability can be simply improved by using parallel redundant desorbent pumps. Failure of the feed pump in the recommended configuration results in diluted insulin product but no HMWP impurity contamination or yield loss. The zone II pump prevents, in the event of its failure, pressure build up and possible collapse of the fragile stationary phase. The zone II pump allows a higher productivity operation than an extract pump configuration, since its maximum pressure drop is lower for a given set of operating conditions. Failure of the zone II pump will result in HMWP impurity contamination of the insulin product if the SMB is allowed to continue in the degraded state for more than half a step-time.

Table 1. Ranking Criteria

Ranking/ Index	Severity	Occurrence	Detection
9	Catastrophic	Inevitable	Uncertain
7	Critical	Highly probable	Remote chance
5	Moderate	Probable	Likely
3	Marginal	Remote	Highly likely
1	Negligible	Extremely remote	Certain

Analysis Methodology

The failure analysis methodology used in this study is first explained, followed by a discussion on the different zone and pump configurations studied here and the associated pump failure modes and effects. Next, details of the column pressure-drop calculation and the simulation tool used for illustrating the dynamic concentration waves in the system are presented. Finally, the particulars of the insulin size exclusion system are presented.

Failure analysis

Failure analysis is an iterative design method used to manage risk.[21-23] Failure analysis identifies, ranks, and eliminates risks to improve product quality, reliability, and safety. It helps to identify and remove waste and redundancy, identify diagnostic, repair, and maintenance procedures, select alternative designs, identify areas for improvement, and reduce rework and design time.

Failure analysis usually includes a series of steps.[23] The system and objectives are first defined; the failure modes of the system or its components are then identified. The cause of each failure mode is determined. The impact and severity of each particular failure mode is assessed and its occurrence is estimated. Next, the system detection capability for the particular effect is assessed. The failure modes are then ranked according to their Risk Priority Number or RPN, which is just a product of Severity (S), Occurrence (O), and Detection (D). Failure modes with higher RPNs or high severity receive more attention. The RPN can be quantitative if data are available; otherwise, expert judgment is used. For the purpose of this work, the ranking criteria in Table 1 are used. Finally, design changes and corrective or preventative actions are carried out to avoid, if not eliminate, the failure causes. If the failure cause cannot be eliminated, more detection capability or testing to detect the failure earlier will be necessary. If detection is impossible or too costly, design changes or contingency plans may be needed to reduce the failure impact.

The SMB equipment includes valves, pumps, columns, fittings, control unit, sensors, and tanks (Table 2). Sensors include flowmeters, pressure gages, and detectors. The detectors, such as UV detectors, can provide quick reading of the process performance. Alternative detection with online HPLC is much more accurate, but costly and with delayed results. Online HPLC may be needed if the product specification requires uncompromised purity.[4]

The components of the SMB system are listed in Table 2 with estimated RPN calculated from our cumulative laboratory

Table 2. Estimated Risk Priority Number for SMB Process Components and Inputs

Component (C)/Input (I)	Severity	Occurrence	Detection	RPN	Ranking
Pumps (C)	7	5	5	175	Critical
Valves (C)	7	5	5	175	Critical
Column & SP (C)	7	5	5	175	Critical
Sensors (C)	5	5	5	125	Moderate
Fittings (C)	5	3	7	105	Moderate
Desorbent (I)	7	1	7	49	Non-critical
Control Unit (C)	7	1	5	35	Non-critical
Feed (I)	7	1	3	21	Non-critical
Tanks (C)	5	1	3	15	Non-critical
Power (I)	3	1	1	3	Non-critical

SP = Stationary Phase, RPN = Risk Priority Number.

experiences and through discussions with SMB vendors and industrial users. Three risk categories can be considered: criticals, moderates, and noncriticals. The critical components are the pumps, valves, and columns packed with the stationary phase. Pump performance directly affects the purity and yield of the separation. Errors in valve performance can easily lead to high pressure in the system. The qualities of the stationary phase, desorbent, and feed affect the separation directly.

In this study, we will focus only on a single pump failure and how it helps select alternative SMB configurations. We will leave the remaining failure modes for future work. The objectives of the analysis are to minimize yield loss of the expensive product, to prevent product loss to the impurity streams, and to minimize contamination of the insulin product stream. A failure's effects, detections, and responses are dependent on their temporal and spatial relations within the system, the zone configuration, and the valve and pump arrangements. Thus, careful selection of the system configuration early on can simplify subsequent analyses.

Zone and pump configurations

We will study three different zone configurations (Figures 1a-c): the four-zone closed-loop SMB, the four-zone open-loop SMB, and the three-zone open-loop SMB. A four-zone open-loop system essentially does not recycle flow back from zone IV into zone I. The open-loop prevents wrap-around of unknown low affinity impurities into the extract product stream. More desorbent is now needed to replace the recycle from zone IV.

The three-zone SMB removes zone IV from the four-zone open-loop SMB. The three-zone SMB has a number of benefits: fewer pumps, valves, and columns are required, resulting in space and cost savings, easier control and diagnostics, improved reliability, and higher productivity. Furthermore, the shorter residence time of the raffinate components[9] reduces the likelihood of aggregation and fouling within the columns. The trade-offs are the higher desorbent consumption and higher raffinate dilution. Nevertheless, for a high-value product, the above benefits easily offset the cost of additional desorbent consumption.

Pumps serve to maintain the specified flowrates within the columns. In conventional SMB, the pumps have constant flowrates. Certain SMB procedures require turning on and off the pumps frequently[11] or frequent changes in flowrates within a step-time.[24] Our analysis will focus on constant flowrate systems at steady-state, and failures that do not involve starting and stopping the pumps.

A zone pump directly controls the flowrate leading into a zone. Part of the flow from the previous zone is pumped into the next zone, while the remaining flow is collected as an outlet stream. Alternatively, an outlet pump can withdraw between two zones (Figure 1a). It has been shown that zone pumps are more robust than outlet pumps[6]; flowrate variation in a zone pump affects the system performance substantially less than an outlet pump. Zone pumps, however, can introduce additional extra-column dead volume, which must be taken into account in the operating design to minimize loss of yield and purity.[20]

Nine pump configurations are analyzed here (Figure 1 and Table 3). In all configurations, the feed and desorbent pumps act as input pumps controlling two inlet streams into the SMB. The nature of the open-loop SMB allows the desorbent pump to directly control the zone I flowrate. Once one of the internal zone flowrates is controlled, the remaining zone flowrates may

Table 3. System Description and Maximum System Pressure in kPa Observed for Each Failure Case

System			Maximum System Pressure for Single Pump Failure (kPa)				
Configuration	No.	Pumps	No failure	Desorbent	Extract/ Zone II	Feed	Raffinate/ Zone IV
Four-zone closed-loop	1	D, ZII, F, ZIV	46	**	**	46	**
	2	D, ZII, F, R	83	**	**	46	119
	3	D, E, F, ZIV	83	**	133	70	83
Four-zone open-loop	4	D, ZII, F, ZIV	38	**	**	34	38
	5	D, ZII, F, R	50	**	**	34	63
	6	D, E, F, ZIV	72	**	121	59	72
	7	D, E, F, R	83	**	154	149	97
Three-zone open-loop	8	D, ZII, F	38	**	34	34	N/A
	9	D, E, F	72	**	121	59	N/A

D = Desorbent pump, E = Extract pump, F = Feed pump, R = Raffinate pump, ZII = Zone II pump, ZIV = Zone IV pump.
**Maximum system pressure not determined since system mass output is higher than its input, resulting in the columns drawing air eventually.

be controlled by outlet or zone pumps. The primary choices thus lie between using an extract or a zone II pump, and a raffinate or a zone IV pump.

A flowmeter is placed directly after each pump in the nine configurations. An additional flowmeter is placed at the zone IV outlet of the four-zone SMB, and at the raffinate outlet of the three-zone SMB. Pressure gages are placed after each inlet and zone pump, and before each outlet pump. Detectors are placed at each exit. The failure analysis will later show a better placement of these sensors (Figure 1d).

Pump failure modes and effects

In SMB, the pumps maintain the liquid flowrates in the columns at the designed operating values. Thus, the major pump failure modes are no flow through a pump and incorrect or fluctuating pump flowrates. We will focus only on the no flow through a pump in this study.

The failure cause of the no flow through a pump may include loss of power to the pump; incorrect signal from pump controller or flowmeter; internal pump failure such as motor failure and piston/valve assembly failure; blocked pump inlet or outlet as a result of lodged particle, fractured tubing, or fittings; and inlet tanks running dry. Reliability can be improved by simple design actions, including the use of redundant power sources, tank level indicators, the selection of highly reliable pumps with pre-pump filters, judicious placement of tubing, and the use of reliable, well-maintained flowmeters.

High pressure in the columns may lead to a collapse of the stationary phase and the subsequent loss of entrapped product in the columns. Stationary phase collapse occurs progressively or catastrophically as a result of particle deformation or breakage from increasing pressure. Column pressure may increase from increased flowrate or increased downflow resistance such as blocked frits and protein gelation.[25] A progressive collapse results in reduction of the bed void fraction.[26] This, in turn, shifts the concentration bands in the columns substantially, resulting in degradation of the system performance. Recovery of the remaining solutes in the collapsed columns is then best achieved through individual column elution rather than through the regular or fast SMB shutdown mode.[11] The collected material can then be re-purified later.

Certain failures, such as the desorbent pump failures, if not detected immediately, will result in drawing air into the columns as more fluid is being pumped out of the SMB than is being replenished. This failure will result in a cracked gel with entrapped air pockets in the columns. The columns would have to be regenerated and repacked. Otherwise, channeling and loss of resolution would be encountered during separation.

Calculation of pressure drop

The Sephadex G50 gel used for insulin purification has a low pressure limit (~103 kPa). The operating flowrates are limited by the maximum pressure drop. Each particular configuration has a different maximum operating pressure even for similar operating zone flowrates. Likewise, each failure event would result in a new set of flowrates and corresponding maximum pressure drop.

The pressure drop from the flow through a packed bed is calculated from the Ergun equation[27]:

$$\Delta P = \frac{150 L u_0 \mu (1-\varepsilon_b)^2}{d_p^2 \varepsilon_b^2} + \frac{1.75 L u_0^2 \rho (1-\varepsilon_b)}{d_p \varepsilon_b}$$

where ε_b is the inter-particle porosity, u_o is the interstitial velocity, d_p is the particle size, L is the bed length, μ is the mobile phase viscosity, and ρ is the mobile phase density.

VErsatile Reaction and SEparation Simulator (VERSE)

VErsatile Reaction and SEparation simulator (VERSE) is used to examine the delayed effects of the failure on the concentration profiles and histories. VERSE replaces time-consuming and expensive experiments with their virtual equivalents. VERSE generated column profiles and histories are useful for understanding the dynamic behavior of complex SMB processes.[8,9] VERSE, a detailed rate model, takes into account dispersion, film mass transfer resistance, adsorption, size exclusion, reactions, pore diffusion, and surface diffusion.[28] It has been used successfully to quickly and inexpensively simulate batch, carousel, and SMB processes, including the size exclusion SMB purification of insulin[4-12] among other processes.[3,13,15,16,20,29,30]

SMB operating conditions and intrinsic parameters

We selected the insulin purification reported as Ring I Run 2 experimental conditions in Xie et al.[4] as our benchmark. In that particular study, insulin was separated from the HMWP in the first ring, while zinc chloride was allowed to migrate freely. Zinc chloride is then removed from insulin in the second ring. We will limit our study to the first ring only.

The operating conditions used here are determined from the standing wave analysis for nonideal (with significant mass transfer effects) and linear isotherm system.[29] The design has been extended to the more robust pinched wave design.[6] This new design method takes into account expected fluctuations in the operating parameters and variations in the intrinsic parameters. We will, however, restrict our operating conditions to the standing wave design to illustrate the maximum impact of a single pump failure.

Table 4 lists the verified parameters used in all the simulations, while Table 5 lists the operating conditions and results of the benchmarks. The open-loop system has higher purities but also higher desorbent consumption. Productivity is higher in the three-zone than the four-zone. Since insulin is the extract product, yield remains identical in all configurations.

Results and Discussion

Each pump failure in SMB results in different changes in the zone flowrates. The changes depend on the zone and pump configurations. The nine configurations (Figures 1a-c) result in a large number of different pump failures. Some of the pump failures in different configurations result in a similar set of flowrates and, correspondingly, a similar set of pressure drops, dynamic column profiles, and outlet histories. For this reason, we will organize the results in terms of the six different pumps, starting with the inlet pumps (desorbent and feed), then the outlet pumps (extract and raffinate), and finally, the zone pumps (zones II and IV). For each particular pump type, we will present selected configurations as representative examples

Table 4. Parameters Used in Simulations

System Parameters†				
Column Information				
L_c (cm)	i.d. (cm)	ε_b	ε_p	DV (cm^3)
13.7	5.1	0.35	0.89	10.4

Size Exclusion Factors, Ke		
HMWP	Insulin	$ZnCl_2$
0.19	0.74*	0.99

Mass Transfer Parameters			
	HMWP	Insulin	$ZnCl_2$
D_∞ (cm^2/min)‡	4.80×10^{-5}	5.49×10^{-5}	3.96×10^{-4}
D_p (cm^2/min)‡	2.00×10^{-5}	2.29×10^{-5}	1.65×10^{-4}
K_f (cm/min)	Wilson and Geankoplis correlation[31]		
E_b (cm^2/min)	Chung and Wen correlation[32]**		

Numerical Parameters	
Axial elements per column	50
Axial collocation points	4
Particle collocation points	2
Absolute tolerance	0.0001
Relative tolerance	0.001

L_c = Single column length, i.d. = Inner diameter, DV = Dead volume per column, D_∞ = Molecular diffusivity, D_p = Intraparticle diffusivity, K_f = Lumped mass-transfer coefficient, E_b = Axial dispersion coefficient.
†Stationary phase is Sephadex G50 and mobile phase is 1N acetic acid.
* Apparent *Ke* for insulin is 0.74.
**In Zone III, a multiple of 40 times E_b predicted from Chung and Wen[32] is used for Insulin to account for fronting.
‡Estimated from Wilke and Chang correlation.[33]

and discuss the failure effects, failure detection, and corrective actions.

We will first look at the immediate flowrate and pressure-drop changes from each pump failure, followed by the delayed failure effects: the dynamic changes in the column profiles and outlet histories. We will compare the failure effect against that of the system without any pump failure. In the simulations, it is assumed that there were no changes in the system intrinsic properties for all cases, and that the system was continuously operated in the degraded state.

Finally, we will recommend a zone and pump configuration for insulin purification. We will also repeat the failure analysis for the recommended configuration and include the time windows to recover completely from the degraded operational states.

Flowmeter placement in SMB

Each pump failure in the different configurations results in at least one flowmeter registering a change. However, the flowmeter placements in the configurations with at least one zone pump (Configurations 1 to 6, and 8) have one drawback: the flowmeters do not provide mass balance checks for the system.

A rearrangement of the flowmeters from the zone pumps to the outlets would be more beneficial. The flowmeters should be placed just before the detectors. This rearrangement allows calculation of the system mass balance and at least two independent checks for any pump-related changes of the pump flowrates, thus improving the detection capability of the system.

In essence, a flowmeter is required at each SMB inlet and outlet. Closed-loop systems require an additional zone flowmeter. A four-zone closed loop SMB requires five flowmeters. A four-zone open-loop SMB requires five flowmeters, and a three-zone open-loop SMB requires four flowmeters.

Impact of pump failure on maximum pressure drop

The different configurations have different maximum pressure drops even for a similar set of operating flowrates (Table 5). The maximum pressure drops in each system without any pump failure and for each single pump failure are listed in Table 3. It is assumed that the valves and fittings do not introduce any significant resistance.

The use of zone pumps results in a lower maximum pressure drop for all comparable cases. Configurations 4 and 8, which are both open-loops and use zone pumps only, have the lowest maximum pressure drop. Configuration 1, which uses two zone pumps but is closed-loop, has the next lowest pressure drop. In a pressure-limited system such as this, a lower maximum pressure drop implies a more robust system, and that higher feedflow flowrates are still possible. Higher feed flowrates result in higher productivities. Thus, in short, for a pressure-limited system, the productivity can be improved by selecting zone pumps instead of outlet pumps, and open-loop SMB instead of closed-loop SMB.

Failures of the outlet pumps lead to increases in the maximum pressure drops (Table 3). Failures in Configurations 1, 4, and 8, which do not have any outlet pump, do not result in overpressure and thus avoid the possibility of stationary phase collapse and the subsequent yield loss. Configuration 8 is, however, more reliable than the others since it has only three pumps.

The flowmeters and pressure gages allow immediate detection of pump failures. In all pump failure cases for all configurations, a similar set of corrective actions is recommended: Upon immediate detection of the pump failure, either through the pressure or flowrate changes, the SMB operation should be frozen in place—the pumps stopped and the valve position frozen. The failure cause should be identified, isolated, and

Table 5. Operating Conditions and Results of Benchmarks

Zone and Pump Configuration	2-2-4-2 Closed-Loop	2-2-4-2 Open-Loop	2-2-4 Open-Loop
Configuration No.	1-3	4-7	8, 9
Zone Flowrates (cm^3/min)			
Zone I	8.49	8.49	8.49
Zone II	5.14	5.14	5.14
Zone III	7.39	7.39	7.39
Zone IV	5.03	5.03	N/A
Inlet and Outlet Flowrates (cm^3/min)			
Feed	2.25	2.25	2.25
Desorbent	3.46	8.48	8.48
Raffinate	2.36	2.36	2.36
Extract	3.35	3.35	3.35
Switching time (min)	27.4	27.4	27.4
Feed Concentration (g/L)			
Insulin	83.5	83.5	83.5
HMWP	0.023	0.023	0.023
$ZnCl_2$	0.315	0.315	0.315
Insulin extract concentration	56.07	56.07	56.07
Insulin purity (%)	99.68	99.72	99.72
Insulin yield (%)	99.96	99.96	99.96
Productivity (L/h · 100L BV)	4.82	4.82	6.03
Solvent consumption (L/kg Insulin)	18.5	45.1	45.1

corrected. The system can then be restarted from the frozen step-time. If the pressure gages, after restarting, record a higher than normal operating pressure, the stationary phase may have collapsed. It is best then to recover the remaining solutes in the columns for re-purification and to replace the columns.

Failure of the flowmeters and pressure gages, or their non-existence, results in continued operation in the degraded state after pump failure. Dynamics of the degraded state are compared against the benchmark cases to show the delayed failure effects.

Dynamics of benchmarks without pump failure

The three different zone configurations result in different column profiles and histories (Figure 2) even for a similar set of operating conditions (Table 5). We will briefly examine the expected steady-state behavior without pump failure before proceeding to the dynamics of the single pump failures. We choose the 100.5 step-time as the occurrence point of failure.

Figure 2a shows the column profile and the outlet histories for the four-zone closed-loop SMB (Configurations 1-3). The standing wave design confined insulin in zones I to III and HMWP in zones II to IV. Zinc chloride is allowed to wrap-around, resulting in the multiple plateaus. In the extract history, insulin forms a plateau at the start of each switch that drops off sharply as the trailing insulin wave moves past the extract port. This behavior repeats itself in each step, and a corresponding extract chromatogram can be observed with an online UV detector. The raffinate history shows the constant concentration of HMWP, the breakthrough, and the subsequent late peaking of the insulin front.

The profiles and histories of insulin and HMWP shown in Figure 2b for the four-zone open-loop SMB (Configurations 4-7) are similar to the four-zone closed-loop SMB since their confined zones are not affected by the open-loop discontinuity. The discontinuity, however, prevents wrap-around of the zinc chloride.

Figure 2c shows the column profiles and raffinate history for the three-zone open-loop SMB (Configurations 8 and 9). As expected, the profile for insulin is similar to the other configurations. However, both zinc chloride and HMWP are affected by the loss of zone IV. The resulting difference in the raffinate history is easier to understand if we were to picture the column profiles for both the four-zone open-loop and three-zone open-loop SMBs just before and after a switch at periodic steady state. For the four-zone case, the last column in zone III would see, after the switch, a column saturated with HMWP; while for the three-zone case, a column with some zinc chloride is introduced from zone I.

Pump failures change the column profiles and observable outlet histories. Careful monitoring of the SMB outlets can thus help diagnose failure within the system. In practice, the detectors suffer a delay as a result of the dead volume encountered by the outlet stream leaving the SMB system. This effect is not included in the analysis since the delay is expected to be very small for a well-designed SMB unit.

Desorbent pump failure

Failure of the desorbent pump, for all configurations, results in air being drawn into the columns through one of the outlet ports or flow reversal in the outlet streams. Reversed zone flows in the open-loop systems are also possible, resulting in HMWP contamination of the purified extract product. To prevent the flow reversal, Back Pressure Regulators (BPR), which act as check valves, can be placed at the outlets. Insulin will accumulate in the system and eventually elute out through the raffinate or the zone IV outlet.

Late detection of desorbent pump failure occurs when the waste stream detectors observe insulin penetration or the extract detector observes HMWP contamination. At this point, air may have been drawn into the columns, leading to channeling and possible loss of product still trapped in the stationary phase. Each column should then be eluted individually. The recovered effluents can be re-purified later. The columns should be replaced.

The recommended corrective action, elution of the individual columns, requires the availability of a second desorbent pump or a quick fix of the original desorbent pump. Since the desorbent pump is critical for recovering entrapped insulin, a spare desorbent pump is recommended for quick insulin recovery.

Feed pump failure

Feed pump failures for the different configurations result in two distinct sets of dynamic behaviors. The first set is exemplified by Configuration 1, shown in Figure 3. A feed pump failure in Configuration 3 has exactly the same dynamic profile and history since their degraded flowrates are similar. The remaining configurations, except Configuration 2, have qualitatively similar dynamics. The dynamic effect of this failure mode is similar to that of the fast shutdown procedure.[11]

In the dynamic column profile of the feed pump failure of Configuration 1 (Figure 3a), the insulin front moves towards the extract port. The resulting insulin product is diluted but not contaminated with HMWP; HMWP remains confined within zones II to IV. The product yield loss is virtually zero. Each component decays within its original concentration band.

Failure detection occurs when the extract history (Figure 3b) shows a faster drop-off of the insulin plateau, which itself quickly decays away in a few steps. The raffinate history shows a quick disappearance of the insulin peak.

Upon detection of the feed pump failure, the SMB operation should be stopped, and the pump failure cause identified, isolated, and corrected. The system can then be restarted from the frozen step-time. Restarting the system from feed pump failures in Configuration 1 is possible because the designated standing waves did not migrate away from their confinement zones. This unique feature allows all open-loop SMBs and closed-loop SMBs with zone IV pumps to completely recover from a feed pump failure. This is illustrated for the recommended pump configuration later.

The feed pump failure in Configuration 2 uniquely results in a decrease in its zone I flowrate. In the other configurations, either the open-loop or a zone IV prevents the flowrate change from propagating to zone I. The change in zone I flowrate in Configuration 2 forces the insulin in zone I to travel slower than the port velocity, resulting in insulin wrapping backwards (Figure 4a). Insulin is eventually lost to the raffinate waste stream (Figure 4b). HMWP merely decays within its concentration band and, thus, does not con-

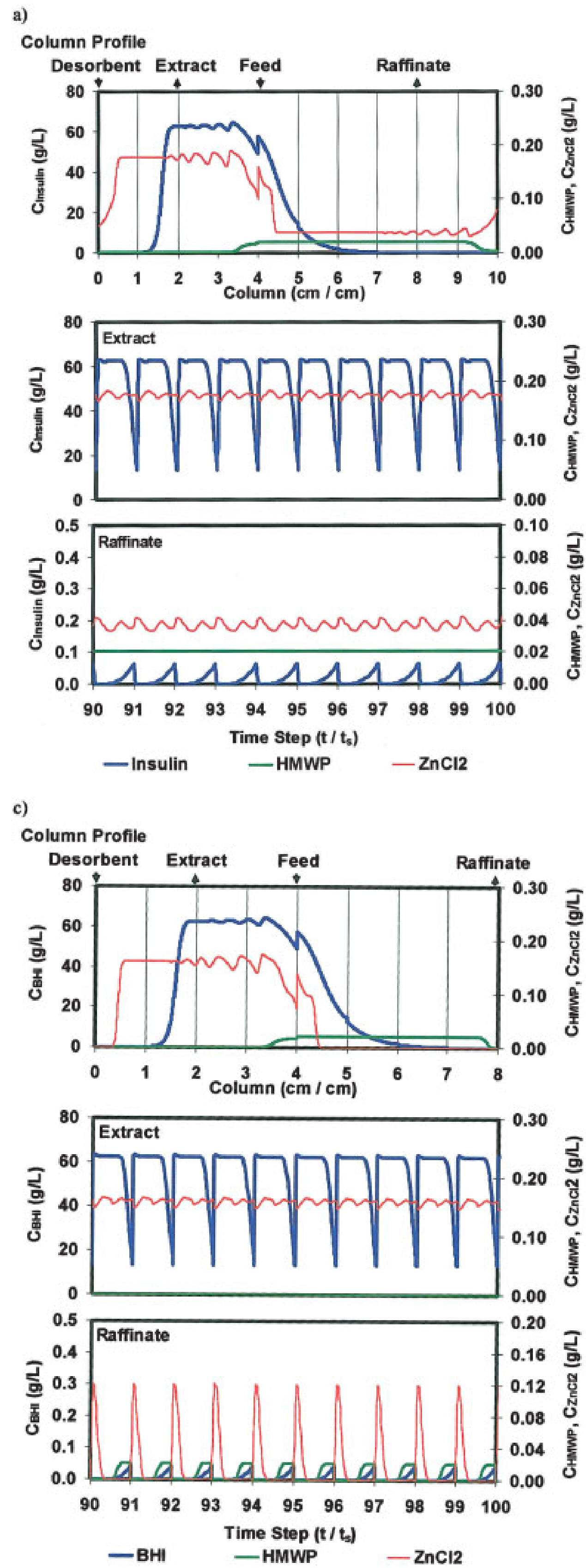

Figure 2. Mid-step column profiles and steady state histories of benchmarks without any pump failure.

(a) Four-zone closed-loop SMB (Configurations 1-3), (b) Four-zone open-loop SMB (Configurations 4-7), and (c) Three-zone open-loop SMB (Configurations 8-9). (t_s stands for switching time.) [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

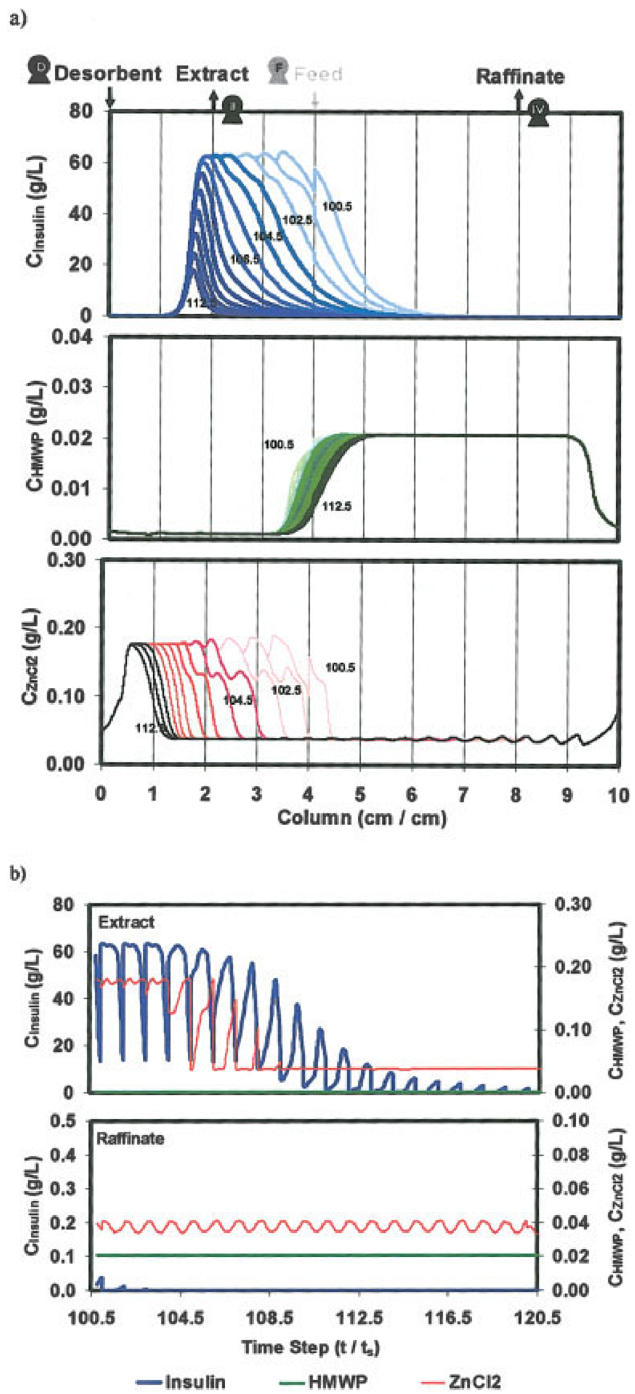

Figure 3. Feed pump failure at 100.5 steps in Configuration 1 (desorbent, zone II, feed, and zone IV pumps).

(a) Column profiles at mid-steps and (b) Extract and raffinate histories. (stands for a pump; light-colored pumps and inlets or outlets indicate pump failure.) [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

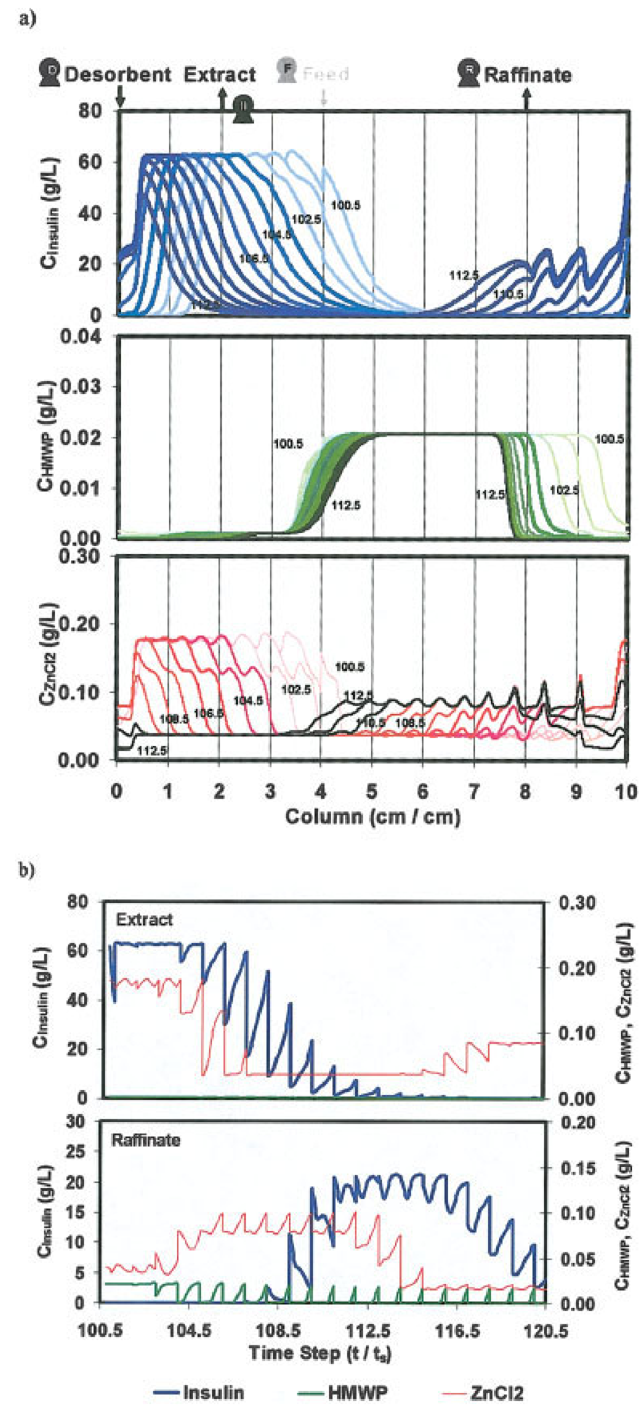

Figure 4. Feed pump failure at 100.5 steps in Configuration 2 (desorbent, zone II, feed, and raffinate pumps).

(a) Column profiles at mid-steps and (b) Extract and raffinate histories. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

taminate the extract product. Feed pump failure in Configuration 2 results in significant yield loss but no HMWP contamination of the extract product.

Extract pump failure

Extract pump failures, in essence, remove the product port. All solutes will eventually leave through the remaining ports. Figure 5 shows the extract pump failure in Configuration 3, which changes the zone II flowrate to that of zone I, and

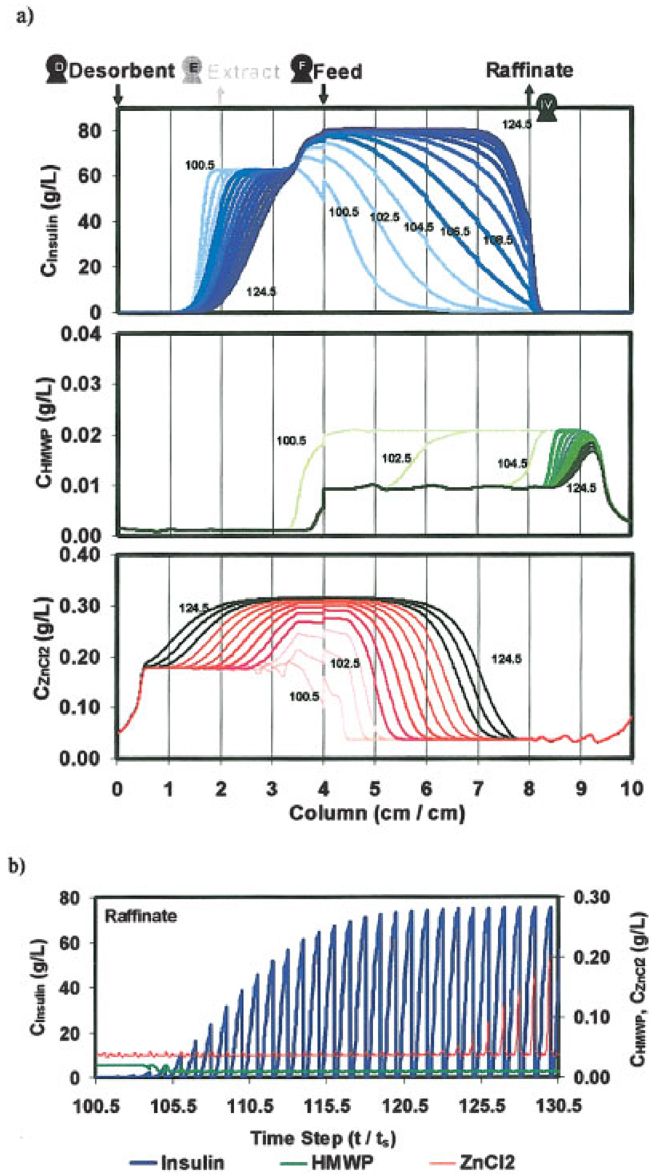

Figure 5. Extract pump failure at 100.5 steps in Configuration 3 (desorbent, extract, feed, and zone IV pumps).

(a) Column profiles at every second mid-step and (b) Raffinate history. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

increases the zone III flowrate. HMWP thus moves forward and is pinched in zone II. Insulin migrates towards the feed port and stands in zone II instead of zone I. Insulin will penetrate the raffinate product within one switching time, as observed in the raffinate history. In Configuration 3, the zone IV pump holds zone IV to its design flowrate; thus, insulin and HMWP do not wrap forward. In short, extract pump failures result in complete loss of insulin to the raffinate but no HMWP contamination of the extract.

Failure detection occurs when the extract detector does not detect a drop-off of the insulin concentration at the expected two-thirds of the time-step as before (Figure 2). Without flow, the extract will merely measure a static reading. The HMWP changes and the later insulin breakthrough at the raffinate (Figure 5b) provide further evidence of the failure event.

If the failure mode is detected late, the columns, as discussed earlier, would have undergone much higher pressure than normal for a substantial period. The system intrinsic parameters may have shifted substantially. The possibility of stationary phase collapse is high at that point, and it is best to conservatively elute each column individually. The stationary phase should be replaced after removal of the solutes.

Raffinate pump failure

Raffinate pump failure in the closed-loop system prevents HMWP removal, resulting in HMWP contamination of the product. The system should be frozen upon failure detection, and the failure identified, isolated, and corrected. The solutes should then be recovered through individual column elution and the columns replaced.

In the four-zone open-loop configurations, only the zone IV flowrate is affected by raffinate pump failures. HMWP, not standing now, moves forward and is collected in the zone IV outlet. The column profiles in zones I, II, and III (not shown) are similar to their benchmarks (Figure 2b). The loss of zone IV in the open-loop system does not affect purity or yield of the extract product. In fact, pressure permitting, the SMB can be continuously operated at the degraded state. The marginal role of zone IV indicates that the three-zone open-loop SMB is a better choice to improve both productivity and system robustness.

Zone II pump failure

Zone II pump failure in the three-zone Configuration 8 is illustrated in Figure 6. The extract flowrate is now equal to that of zone I, and zone III to that of the feed. Upon switching, the loaded column from zone III remains stagnant in zone II and is eventually eluted completely through the extract port.

Zone II pump failures in the four-zone systems, namely Configurations 1, 2, 4, and 5, however, result in air being drawn into the system as more solution is withdrawn than is replenished. As before, BPRs can be installed to prevent backflow from the outlets into the system. As in Configuration 8, columns in the stagnant zone II will migrate upstream to zone I and elute out through the extract; HMWP contaminates the purified insulin in the extract product tank if the zone II pump fails in Configurations 1, 2, 4, and 5, and the SMB is continuously operated in the degraded state.

For all zone II pump failures, failure detections occur when the extracts observe unexpected insulin or zinc chloride histories and HMWP contamination. The system should be frozen, and the failure cause identified, isolated, and corrected. The solutes in the columns should be recovered and repurified, and the columns replaced.

Zone IV pump failure

The loss of the zone IV pump in the four-zone closed-loop Configuration 1 results in air being drawn into the system. The loss of the zone IV pump in the four-zone closed-loop Configuration 3 results in a decrease in all the zone flowrates and eventual product contamination and yield loss. Upon detection of such failures, the system should be frozen, and the cause

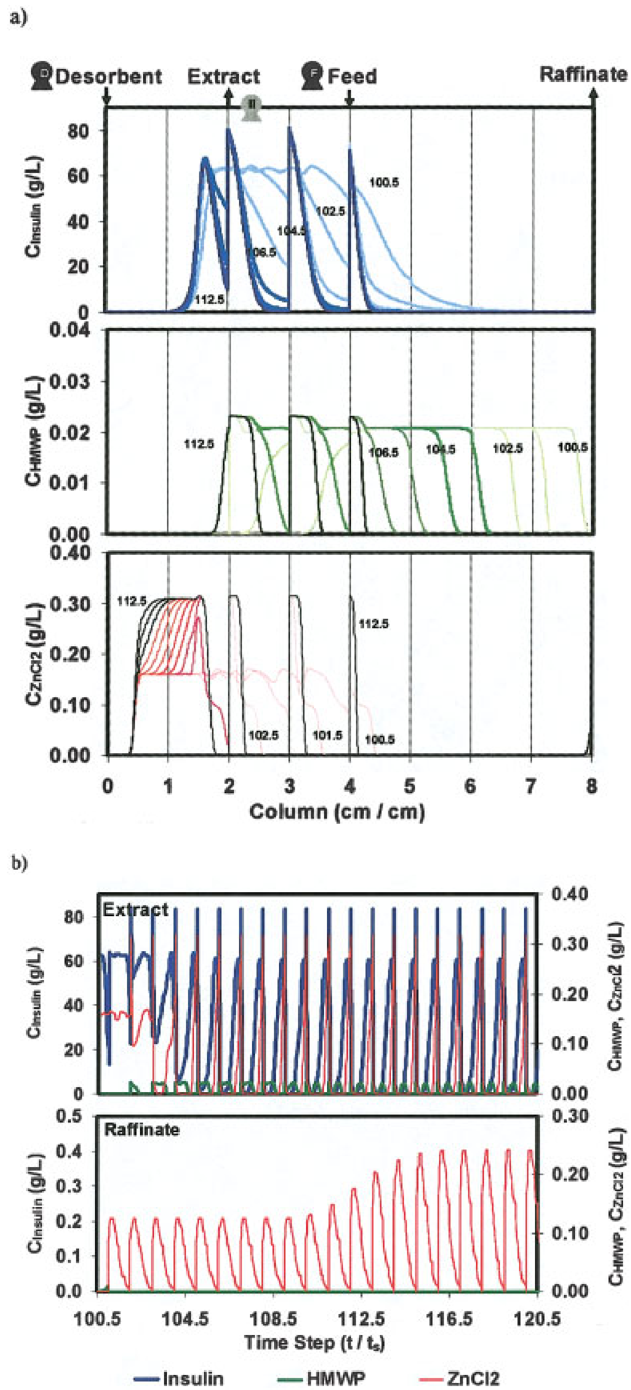

Figure 6. Zone II pump failure at 100.5 steps in Configuration 8 (desorbent, zone II, and feed pumps).

(a) Column profiles at mid-steps and (b) Extract and raffinate histories. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

identified and isolated. The solutes should be recovered from the columns and repurified.

In the open-loop systems of Configurations 4, 5, and 6, the zone IV pump failures would lead to no flow within the columns in zone IV. HMWP gets washed out in the raffinate completely, forming late peaks instead of a smooth history. Zinc chloride, wrapping backwards, does not get washed out in the zone IV outlet, but is now trapped within the static zone IV, and later eluted out through the raffinate. The first three zones in the SMB are not much affected since only the last column in zone III inherits the static columns from zone IV, which are then completely eluted within a single step-time.

For zone IV pump failures in the open-loop configurations, the system can continuously operate in the degraded state without affecting the extract product yield and purity. This, of course, implies that zone IV in the open-loop system, as in the raffinate pump failure, plays a marginal role and can be safely removed.

Summary of single pump failures in size exclusion SMB purification of insulin

Failure of the desorbent pump is critical since air will be drawn into the columns if the SMB operation is not stopped immediately. Online elution (instead of offline elution) to recover the entrapped products in the columns is also not possible without the desorbent pump. The desorbent pump plays a critical role, and a spare desorbent pump is thus recommended.

Feed pump failure is, in general, benign and merely dilutes the extract product. Feed pump failure in four-zone, closed-loop Configuration 2, however, results in yield loss and product contamination.

Extract pump failure is critical since the gel undergoes high pressure and is likely to collapse. If the operation is not stopped immediately, complete loss of the entrapped products is possible. In comparison, a zone II pump failure results in air being drawn into the four-zone SMB and yield loss in the three-zone SMB; zone II pump failure is also critical. However, the zone II pump failure does not result in gel collapse. Additionally, the zone pump is more robust and allows a higher productivity operation. Thus, we recommend the use of a zone II pump instead of an extract pump in all configurations.

Raffinate pump failures in the closed-loop SMBs can result in gel collapse due to high pressure and product contamination. In the open-loop systems, raffinate pump failures increase the maximum pressure drop slightly but do not affect the product. This result also suggests that accurate raffinate pump flowrate is not critical to the extract product purity and yield. A zone IV pump failure in the open-loop systems is relatively benign. Zone IV pump failure in the closed-loop systems, however, is critical; air is drawn, or product contamination and yield loss occurs. The zone IV pump is thus recommended for the open-loop system.

Without zone IV, the raffinate and zone IV pumps are no longer needed. The three-zone SMB is more robust because it has fewer columns, valves, and pumps, and lower probability of failure. The higher solvent cost is offset by higher productivity, lower system cost, and lower risk of loss of the high value product.

Recommended pump configuration for size exclusion SMB purification of insulin

Based on the results of this study, a three-zone SMB with zone II pump and dual desorbent pumps (Figure 1d) is recommended. The spare desorbent pump allows recovery of entrapped solutes within the columns in the event of any pump failure. This configuration does not allow collapse of the stationary phase in all failure cases, drawing air into the columns only if the failure of the desorbent pump is not detected immediately. Severity of the failures is thus minimized. The flowmeters have also been shifted to allow

Table 6. Failure Detections, Effects and Actions for Single Pump Failure of the Recommended Configuration (Figure 1d)

Pump Failure	Detection	Sensors†	Effects	Actions
Desorbent	Immediate	$FM_{Desorbent} = FM_{Extract} = 0$ $P_{Desorbent} = 0$	No immediate effect	Freeze operation; identify and isolate cause; restart from frozen step time with parallel desorbent pump
Desorbent	Late	Raffinate detector shows insulin penetration into waste stream	Columns draw air Possible loss of product to raffinate outlet	Freeze operation; identify and isolate cause; recover solutes in column for repurification; check raffinate for insulin; check product purity; replace columns; fresh restart
Zone II	Immediate	$FM_{Extract} = 8.49$ $FM_{Raffinate} = 2.25$ P_{ZII} & $P_{ZIII} \downarrow$	No immediate effect	Freeze operation; identify, isolate, and correct cause; restart from frozen step-time
Zone II	Late	Extract detector shows HMWP contamination and late insulin	HMWP contaminates insulin product	Freeze operation; identify, isolate, and correct cause; recover solutes in columns for repurification; check insulin purity; fresh restart
Feed	Immediate	$FM_{Feed} = 0$ $FM_{Raffinate} = 5.14$ P_{ZII} & $P_{ZIII} \downarrow$	No immediate effect	Freeze operation; identify, isolate, and correct cause; restart from frozen step-time
Feed	Late	Extract detector shows decaying insulin history	Results in diluted insulin product	Freeze operation; identify, isolate, and correct cause; restart from frozen step-time

†FM = Flowmeter, P = Pressure gage.

complete mass balance checks and at least two independent readings of each pump failure. Detection capability has thus improved.

The failure analysis of the recommended configuration, taking into account the use of the dual desorbent pumps and the improved flowmeter arrangement, is summarized in Table 6.

Figure 7 shows the dynamic recovery of the SMB after the feed pump failed at the 100.5th step and the system was continuously operated in the degraded state for four switching times. As discussed earlier, restarting the feed pump anytime after failure does not result in yield loss or extract product contamination. As observed, each of the components remains within its original boundaries. Qualitatively similar profiles are observed for different periods of feed pump failure.

The zone II pump failure, however, will result in significant HMWP contamination of the product if the system was operated in the degraded state for more than a half step-time. Figure 8 shows almost complete system recovery within seven steps after the zone II pump failed for two switching times. Without flow in zone II, the HMWP wave is shifted backwards by the periodic forward movement of the ports.

Conclusions

A three-zone SMB with dual desorbent pump, a zone II pump, and a feed pump is recommended for size exclusion purification of insulin. A three-zone SMB uses more desorbent but is operationally simpler and has lower failure risk, higher productivity, lower cost, higher extract purity, and reduced possibility of HMWP fouling.

A flowmeter should be placed at each inlet and outlet to provide redundant flowrates checks and calculation of the mass balance. Closed-loop systems have an addditional zone flowmeter. The pressure gages at each pump outlet and the aforementioned flowmeters provide immediate detections of changes in the flowrates of the system.

The desorbent pump failure in the recommended configuration can result in drawing air into the columns. The use of a redundant desorbent pump is recommended to improve the system reliability and to allow recovery of trapped solutes in case of pump failure. The feed pump failure results in diluted

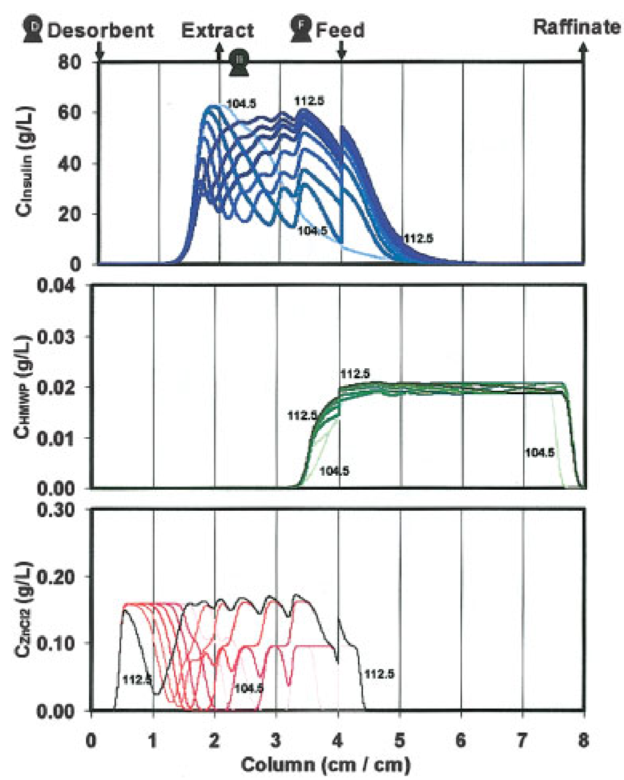

Figure 7. Dynamics of the recovery from feed pump failure in the recommended configuration (Figure 1d).

Failure occurred between 100.5 and 104.5 steps. Feed pump restarted at the 104.5th step. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

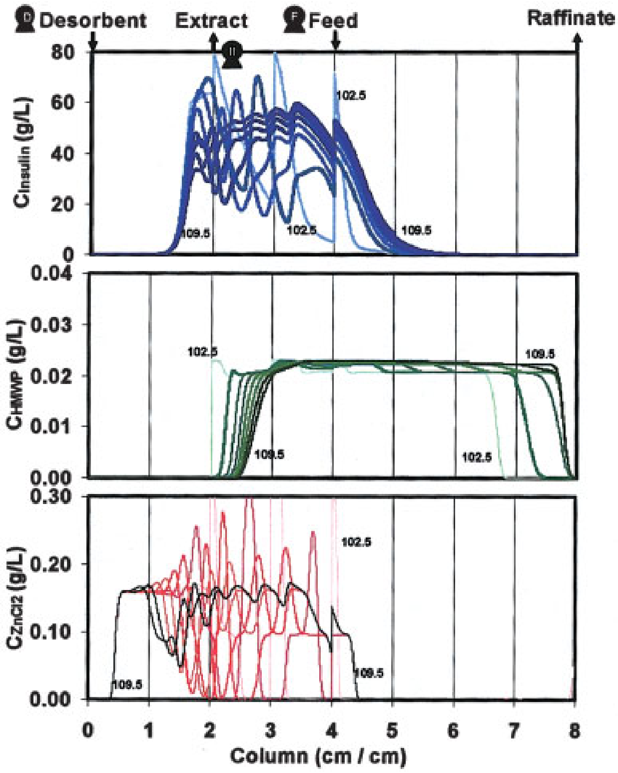

Figure 8. Dynamics of the recovery from zone II pump failure in the recommended configuration (Figure 1d).

Failure occurred between 100.5 and 102.5 steps. Zone II pump restarted at the 102.5th step. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

product, and the system can be restarted anytime after failure without yield loss or product contamination.

The zone II pump failure results in contaminated product, which can be repurified later. The zone II pump instead of the alternative extract pump is recommended because the zone II pump allows the system to operate at higher feed flowrates and does not allow overpressure in the event of pump failures. Zone pumps are also more robust against periodic flowrate fluctuations in the system. In the case of zone II pump failure, the time window for complete recovery without any product contamination is half a step-time.

Failure analysis of single pump failures in different zone and pump configurations helps select between alternate configurations and helps improve SMB reliability. Rate model simulations were successfully used to illustrate and explore the dynamic wave phenomena of each failure. The simulations help determine the failure effects, detections, and corrective actions.

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